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CIRCULATION IN HYPERTENSION

By S. K. Kiseleva

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THE EFFECT OF RESERPINE ON THE CORONARY CIRCULATION
IN HYPERTENSION

[Following is the translation of an article by S. K. Kiseleva entitled "Deystviye Rezerpina na Koronarnoye Krovoobrashcheniye pri Gipertonicheskoy Bolezni" (English version above) in Terapevticheskiy Arkhiv (Therapeutic Archives), Vol. 32, No. 5, Moscow 1960, pages 19-26.]

From the "Barvikh" Clinical Sanatorium (Chief Physician K. A. Galenin; Scientific Director -- Professor K. G. Karasev) of the Fourth Main Administration in the Ministry of Health USSR

Reserpine (serpasil) is a pure alkaloid which was first isolated by Müller, Schlittler, Bein in 1952 from the roots of the Indian bush Rauwolfia serpentina is, at the present time, enjoying great popularity in therapeutic practice and psychiatry both abroad and in the Soviet Union because of its hypotensive and sedative properties. It has been shown by numerous investigations that this alkaloid possess chiefly a central nervous effect (Bein, Bein and others, Winsor, Schneider, Tripod and others, Moyer, N. V. Kaverina and Ye. S. Milovidova and others). More precisely, the topographic

mechanism of the central pharmacological effect of reserpine is the hypothalamic area, the cerebral cortex and the reticular substance of the brain stem (Plummer and others, Gangloff and Monnier, Harrison and Goth).

Experimental studies made by some research workers in the past few years have shown that reserpine acts through the intensified excretion (chiefly by the brain substance) of serotonin, which serves as a mediator in suppressing the activity of the sympathetic nervous system centers (Fletscher and others, Brodie and others).

According to the studies of individual authors, reserpine possess not only a sedative and hypotensive effect but also the capacity of slowing the heart rate and increasing its stroke volume (Gotten and others, Moyer), of increasing the secretion of the gastric juice and increasing the gastric and intestinal peristalsis (Barrett and others, Plummer and others, Moyer, Clark and Schneider, Rider, Schneider and Clark, Kirsner and Ford), inhibiting the function of the thyroid gland and reducing the basal metabolism (Winsor, Moyer), increasing the circulation in the kidney and reducing the renal resistance (S. K. Kiseleva).

We have not encountered either clinical or special experimental studies in either the foreign or the Soviet

literature concerning the effect of reserpine on the coronary circulation. There have been only incidental statements concerning the change in the electrocardiogram in some patients in articles by various authors on the treatment of hypertension with reserpine. Some of them find considerable changes in the electrocardiogram from rauwolfia preparations (Watschinger, Klausgraber) or they find them only in a few patients (Raymond, Kert and others, N. I. Guseva). Others (Lewis and others) found definite electrocardiographic changes in treating angina pectoris with rauwolfia preparations in the direction of an improvement. However, these data are so few and indefinite that it is difficult to gain any specific idea from them concerning the circulation in the coronary vessels of the heart during treatment with reserpine.

The aim of the present communication is to show how the coronary circulation is changed in patients with hypertension when they are treated with reserpine (serpasil) according to the clinical and electrocardiographic data.

There were 330 patients with hypertension (283 men and 47 women) in the second and third stages under our observation (from 1954 through 1958).

With respect to age they were distributed in the

following way: six persons under 40; 100 persons from 41 to 50; 165, from 51 to 60; 38, from 61 to 70; 20, from 71 to 80; one, over 80. The duration of the disease varied from three to 25 years (on the average, nine years). In 204 persons the disease was in the II stage; in 126 persons, in the III stage.

The patients experienced different sensations in the cardiac area. Typical anginal pains with a characteristic radiation and a feeling of "angor animi", making the patients maintain a state of rest, were noted in 115 persons. Sixty-eight patients had pains in the cardiac region and retrosternally of a compressive nature without radiation which were eliminated by validol or nitroglycerin. Twenty-six persons complained of pains in the cardiac region of cutting nature which were relieved by vasodilators. A sensation of weight in the cardiac area, frequently associated with changes in the barometric pressure, was experienced by 14 patients; a sensation of pressure in the cardiac area, by 17. In 90 persons there was no pain syndrome in the cardiac region. Aside from the painful sensations 16 patients complained of palpitation and "stoppage" of the heart. Forty-seven patients had a history of myocardial infarction; nine of them had had repeated infarcts. In

a great majority of patients a dilatation of the left border of the heart was noted to varying degrees with a muffling of the apical sounds as well as accentuation of the second sound over the aorta. In 11 persons a disturbance of rhythm was found in the form of auricular fibrillation; in 10, there were frequent extrasystoles; and in six, sinus arrhythmia. Before treatment the systolic pressure varied from 260 to 140 millimeters of mercury (the average for the entire group was 175 millimeters); the diastolic pressure varied from 140 to 75 millimeters (the average for the entire group was 103 millimeters). The pulse rate was within limits of from 68 to 112 beats a minute (on the average, 78). The electrocardiographic data indicated a disturbance in the coronary circulation in 166 out of 330 patients; in 150, diffuse changes in the myocardium were noted; and in 14, left axis deviation.

All the patients were divided into two groups, of 165 persons each. The same regimen, nutritional and treatment conditions were provided, as much as possible, for every group. The severity of the disease in patients of both groups was also approximately the same. Patients of the first group (1956-1958) were treated with reserpine; those of the second group (1954-1956)

The dose of reserpine varied from 0.1 to 0.25 milligrams two-three times a day (average daily dose, 0.6 milligram). The duration of the treatment, on the average, was 26 days (from 15 to 60 days). Aside from reserpine, during the observation period the patients of the first group did not receive any other antihypertensive agents, and only some of them took laxatives, ascorbic acid, bromides, valerian, and validol or nitroglycerin only when they had pains in the heart.

We should like to present a characterization of patients treated with reserpine (first column) and xanthine preparations (second column) and the results of treatment.

No of patients examined	165	165
No of these who were: men.	137	146
women.	28	19
Average age (in years).	54	52
No of patients according to stage of disease		
II.	105	99
III.	60	66
No of patients		
with history of myocardial in- farction.	26	21
with history of cerebrovascular disorders	22	21
Average duration of treatment (in days)	26	32
Blood pressure (in millimeters of mercury)--average indices		
before treatment.	175/103	178/104
after treatment	136/82	156/94
Pulse rate (number of beats a minute)		
before treatment.	78	78

after treatment	62	74
No of patients in whom pains were observed in the cardiac region characteristic of angina pectoris	95	88
pains of another nature	26	31
no pain.	44	46
No of patients in whom following treatment the pains disappeared.	65	28
decreased	53	67
remained the same	3	21
increased	--	3
No of patients with electrocardiographic changes (before treatment) of the coronary insufficiency type.	87	79
diffuse.	71	79
left axis deviation.	7	7
No of patients in whom after treatment the EKG improved	105 (63.6%)	42 (25.5%)
remained unchanged	45 (27.3%)	84 (50.9%)
worsened	15 (9.1%)	39 (23.6%)

It is characteristic that the blood pressure after reserpine treatment was reduced to a greater extent than after treatment with xanthine preparations. The same interrelationship was noted in the slowing of the pulse and the lessening of the pain syndrome.

Along with the reduction in blood pressure, slowing of the pulse and alleviation or disappearance of the pain syndrome in the cardiac region after treatment with reserpine the general condition improved to varying degrees, sleep became normal, headaches decreased or disappeared, as also did dizziness, in all patients, and in the majority of them, regardless of the stage of the disease, a feeling of "general well-being" appeared.

Following reserpine treatment, on the electrocardio-

grams of the majority of patients an improvement in the coronary circulation was noted. It was expressed in a levelling off of the S-T segment, changes in the T wave in the direction of normalization, chiefly in the chest leads, and an increase in the systolic index. Fig. 1 illustrates the change in the electrocardiogram after reserpine treatment through the example of patient B., age 55, who suffered from hypertension for 12 years and chronic coronary insufficiency against the background of myocardial infarction. In five out of eight patients the extrasystoles disappeared; in three out of four, the sinus arrhythmia. In six patients with auricular fibrillation the rhythm remained irregular, but the rate was considerably reduced (on the average, by 27 beats a minute), the palpitation decreased, and the shortness of breath on walking disappeared.

A deterioration of the electrocardiograms following reserpine treatment occurred in 15 patients from 62 to 81 years of age, in whom general arteriosclerosis was found with predominant involvement of the cerebral vessels and coronary arteries of the heart. In 11 of them a disturbance in the cerebral circulation had been noted in the past; in two, repeated myocardial infarctions. It may be assumed that the degenerative

changes in the myocardium of the patients of this group had gone so deep that the possibilities of improvement of the metabolic processes in it were very limited.

At first glance, the impression may be gained that the pronounced improvement in the electrocardiograms and the disappearance or the lessening of the pain syndrome in the cardiac region of the patients, which we observed, was brought about by the effect of the sanatorium condition, the relaxation itself, the effect of favorable climatic factors, and that the part played by reserpine here is not so essential. Keeping in mind the fact that it is difficult to separate the therapeutic effect from the effect of the sanatorium-protective regimen on the improvement of the coronary circulation, we began the treatment of 22 patients of the first group with reserpine on the 15th-16th day after they arrived at the sanatorium. During these two weeks, against the background of the sanatorium-protective regimen alone, the electrocardiogram improved somewhat in four out of 22 patients; in 15 there were no changes; and in three, it even worsened somewhat. The treatment of these 18 patients with reserpine which was given during the next two to two and a half weeks produced notable changes in the electrocardiographic curves in

the direction of improvement in the myocardial nutrition by the end of treatment in 17 of them. In Fig. 2 an electrocardiogram is shown of one of these patients (patient A., age 56) who suffered from hypertension accompanied by frequent anginal attacks and complicated by a myocardial infarction in the anterior wall and the interventricular septum.

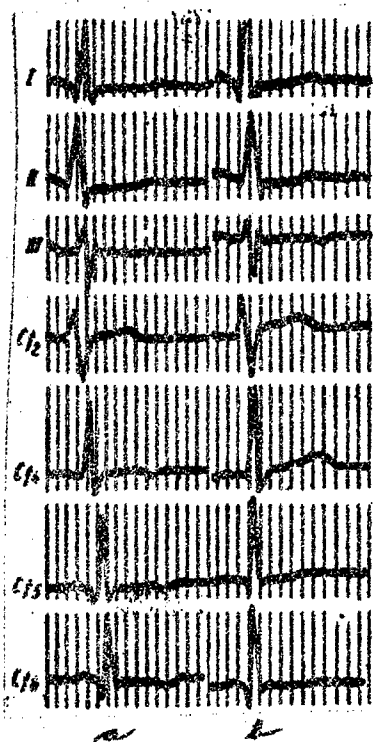


Fig. 1. EKG of Patient B., Who Was Treated with Reserpine.

a--before treatment; b--after treatment.

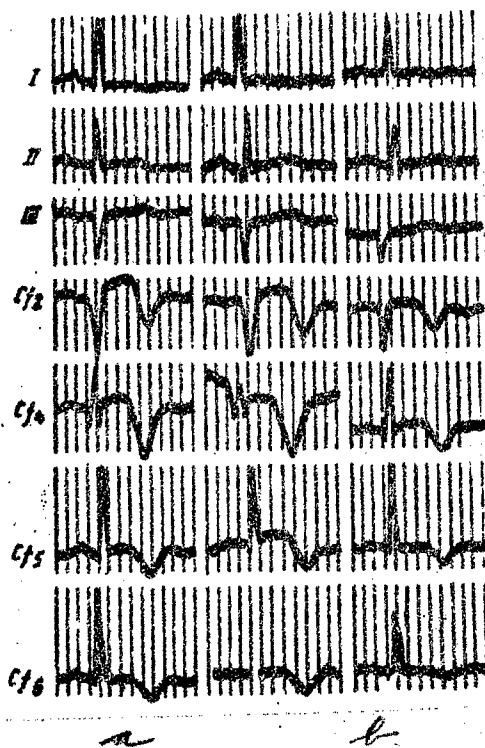


Fig. 2. EKG of Patient A., Who Was Treated with Reserpine.

a--on admission; b--before onset of treatment; c--after treatment.

In 17 patients of this group, in whom as a result of treatment with reserpine the electrocardiogram improved definitely, we continued the electrocardiographic investigation for 15-18 days after treatment was stopped. As a result the following was found: at the time of discharge the electrocardiogram returned to the original level in six patients; in 10 it did not change; and in one patient it deteriorated somewhat (there was a slight deepening of the T_{Cf_5} wave) compared with the electrocardiogram at the time of admission. Of these 17 patients six had been given reserpine treatment a second time, for 15 days. The electrocardiogram changed again in the direction of an improvement in the coronary circulation.

The data presented here convince us quite clearly of the favorable influence of reserpine on the coronary circulation. There is no basis for referring the improvement in the coronary circulation to the improvement of the working conditions of the heart as a result of the lowering of the peripheral arterial pressure. The reduction in the blood pressure after reserpine treatment was noted in 160 out of 165 of our patients, whereas the improvement in the electrocardiogram was noted in only 105. At the same time, in two out of three patients in whom reserpine did not reduce the blood pressure the

electrocardiogram indicated a change in the direction of improvement of myocardial nutrition (tendency toward normalization of the T wave in the standard leads and in the Cf₄₋₅ leads).

Therefore, it should be supposed that the electrocardiographic changes indicating improvement in the coronary circulation of the majority of patients, whom we observed, depend not so much on the reduction in blood pressure as, apparently, on the functional changes in the coronary blood vessels, reduction of the tone of the myocardial arteriole walls under the influence of reserpine. The treatment results of patients of both groups as well as the data presented in Table 1 are convincing evidence of this.

Table 1

Change in the Electrocardiographic Indices in Patients with Hypertensive Disease Complicated by Chronic Coronary Insufficiency after Treatment with Reserpine and Xanthine Preparations

Method of treatment	Change in the electrocardiogram									
	total pts.	ave- age	sex		stage of disease	improve- ment	no change worsening			
			men	women			II	III	No of patients	
Reserpine	87	56	74	13	42	45	54(62.1%)	21(24.1%)	12(13.8%)	
Xanthine preparations	79	54	68	11	40	39	21(26.8%)	34(43%)	24(30.3%)	

In addition, we made observations on the change in the functional adaptability of the coronary blood vessels, under the influence of reserpine, to physical exercise. This is a valuable functional test which determines the condition of the cardiac muscle and coronary circulation. However, since the severity of the patients' conditions did not make it possible to use squatting, walking up a step-stool, etc., that is, the physical tests of the heart which have been adopted clinically, we made use of the simplest method -- terrain cure [graduated walking], which is extensively used and has long enjoyed popularity as an active therapeutic method based on the principle of making increased demands on the cardiac muscle with the easiest conditions for their fulfillment. This test has practically no contraindications, and with a moderate speed of walking and observance of the rhythm it is well tolerated. For the purpose of checking on the effective physical exercise on the functional condition of the myocardium and its arterial network we made use of electrocardiographic examination of the heart, which was performed in 55 patients with chronic coronary insufficiency in each of the two groups. The electrocardiograms were recorded before and immediately after walking, both before treatment was begun and at

the end of the course of treatment in each group of patients. The walks of the sanatorium park were the place where the dosaged walks were taken by the patient. The conditions of the patients were different, and, therefore, we could not give them all the same definitely established walking conditions along definite routes. The walk was dosaged individually for each patient with consideration of his therapeutic status and degree of training, but in each individual case it was absolutely identical both in distance and in time, as well as in tempo before treatment and at the end of reserpine treatment. Such individually dosaged exercise along the park walks with consideration of the functional condition of the cardiovascular system and of the body as a whole did not produce any harm in the patient and never caused any painful sensations in the heart. Experienced methods personnel, treating physicians or therapeutic physical culture physicians observed the walks.

As is seen from Table 2, the dosaged walks before reserpine treatment did not produce any essential electrocardiographic changes in the direction of normalization in the majority of patients. After the use of reserpine and particularly toward the end of the course of treatment this relationship was considerably changed.

In the majority of patients a definite electrocardiographic change in the direction of improvement was noted. In Fig. 3 a change in the electrocardiogram is shown under the influence of the walks after reserpine treatment in patient K., age 49, who suffered from hypertension complicated by a disturbance in the coronary circulation in the area of the anterolateral wall of the myocardium.

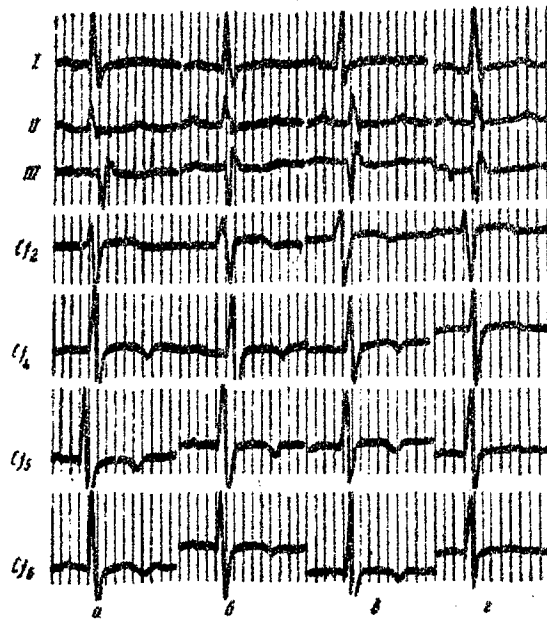


Fig. 3. EKG of Patient K., who was treated with Reserpine.

a--before; b--after walking prior to beginning reserpine treatment; c--before; d--after walking at end of reserpine treatment.

Effect of Treatment on Change in EKG Produced by Physical Exercise in Patients with Hypertension Complicated by Chronic Coronary Insufficiency

① Метод лечения	② Одноразовый прием	③ Средняя доза		④ Токсичность	⑤ Средняя продолжительность	⑥ Назначение электрокардиограммы после завершения процедуры							
		⑦ Возраст	⑧ Число дней			⑨ Число приступов		⑩ Улучшение					
						⑪ Возраст	⑫ Средняя продолжительность		⑬ Число приступов	⑭ Число приступов			
Резервация ⑮	55	49	50	5	33	22	9 (16,4%)	35 (63,6%)	11 (20%)	45 (81,8%)	10 (18,2%)	—	12
Ксантинные препараты ⑯	55	48	51	4	34	21	10 (18,1%)	33 (60%)	12 (21,9%)	21 (38,1%)	25 (45,5%)	9 (16,4%)	14

[illegible]

In the group of patients untreated with reserpine, as is seen from Table 2, the dosaged walks also caused an improvement in the electrocardiograms; however, these changes were not so frequent and substantial as after reserpine treatment.

Therefore, clinical and electrocardiographic observations made before and after dosaged walking in patients with hypertension show the favorable influence of reserpine on the functional adaptability of the coronary vessels to increased demands of physical exercise. In 10 patients, in whom after dosaged walking there was no improvement in the electrocardiogram at the end of the course of treatment, there was, apparently, a difficultly reversible sclerotic lesion of the coronary arteries.

Conclusions

1. Clinical and electrocardiographic methods of investigations of the functional condition of the myocardium serve as a basis for judging the change in the coronary circulation in one direction or another, both at rest and under conditions of physical exercise. In 63.6 percent of the patients with hypertension changes could be detected on the electrocardiogram in the

direction of normalization under the influence of reserpine, which is evidence of the favorable effect of it on the coronary circulation.

2. In 53.7 percent of the patients, who had experienced pains in the cardiac region before treatment, reserpine at the sanatorium eliminated these painful sensations.

3. A decrease or disappearance of anginal pains and improvement of the electrocardiogram under the influence of reserpine are brought about not only by the reduction in the blood pressure but also chiefly by the reduction in the tonic contraction of the arteriole walls of the cardiac muscle, as the result of which the myocardial nutrition is improved, and the metabolic processes in it become normal.

4. In 35 out of 55 patients with hypertension reserpine under sanatorium conditions exerted a beneficial influence on the adaptability of the cardiac muscle to physical exercise. This was expressed in an improvement in the clinical picture of the disease and was confirmed by the beneficial electrocardiographic dynamics.

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